

REMARKS

Claims 6-13, 15, 16, 18, 20-21 and 30-32 are currently pending in this application. Claims 50-54 are newly added. Antecedent support for the newly added claims is found in the original claims, Example I of the application, and throughout the specification.

In the Official Action of April 6, 2004, claims 14 and 18 were objected to as being substantial duplicates of one another. In response to this objection, claim 14 has now been canceled without prejudice. Accordingly, this ground of rejection has now been obviated.

Claims 6, 10-14, 16, 18-21 and 30-32 have been rejected under 35 U.S.C. 103(a) as being obvious over Van Ness et al. (U.S. Patent No. 5,667,976) in view of Grieve et al. (U.S. Patent No. 6,391,569). This ground of rejection is respectfully traversed.

The Examiner states that Van Ness et al. teaches solid supports used for nucleic hybridization assays using polymer coated magnetic beads. The Examiner further states that oligonucleotides can be immobilized on the beads by covalent attachment to serve as nucleic acid probes. It is asserted that beads can be employed free in solution.

The invention described in Van Ness et al. is fundamentally different from the invention described and claimed in the present invention. In Van Ness et al., the oligonucleotides are attached to pre-formed polymer beads by means of covalent attachment of the amine-containing polymer coating on the bead with an amine on the oligonucleotide. The beads of Van Ness et al. have dimensions of from about 0.01 inches to 0.5 inches in diameter. See col. 3, lines 48-62 of the reference.

In contrast, the colloidal particles of the present invention are formed by dispersing a matrix material, such as nitrocellulose, polyvinyl difluoride or activated nylon, using a liquid medium, such as water, and attaching the oligonucleotide to the colloidal particles. The colloidal particles of the present invention are less than about 1 micron (0.000001 meters, or about 0.00004 inches). The particles of the present invention are substantially smaller than the particles of the Van Ness et al. reference. This substantially reduced particle size contributes to the enhanced results achieved by the present invention in comparison to the far larger particles of the prior art. For instance, note Example V of the present invention, illustrating an enhancement in sensitivity, and VI, illustrating the reduction in nitrocellulose levels and the associated

background fluorescence, all in comparison to the prior art. These are dramatic improvements, and are far beyond what may have been achievable as a result of a mere “design choices”.

The Examiner states that a change in particle size is generally recognized as being within the level of ordinary skill in the art. While this may be true for incremental changes in size, it is certainly not the case where a change in particle size represents a difference in kind rather than a difference in degree. For instance, the particles of this present invention are at least 250 times smaller than the particles of the Van Ness et al. reference (0.00004 vs. 0.01). Again, this result cannot be achieved without a technological improvement that is beyond the scope of the prior art.

The Grieve et al. reference has been cited as teaching the immobilization of a protein on a solid support. Applicant notes that newly added claims 50 and 51 are directed to embodiments of the invention wherein the biomolecule is a protein.

Although the Grieve et al. reference has been cited as disclosing an equivalence between oligonucleotides and proteins, it is submitted that there is no such equivalence for purposes of this invention. For instance, oligonucleotides are heat stable and not subject to denaturation. In contrast, proteins are delicate molecules and easily denature under a wide variety of conditions, such as heat, dehydration and perturbation of pH levels. Denaturation of proteins results in a loss of the characteristic 3 dimensional protein shape (i.e. the loss of epitopes), and the loss of antigenicity.

The present invention preserves the natural epitopes on the proteins, even after physical manipulation and drying during processing, which other technologies have been unable to do. This is accomplished by mixing the ingredients of the liquid composition in a slurry, and then spotting the composition onto a suitable support, rather than applying the protein to an immobilized adherent. The protein spot, even after drying, remains fully active, which is a major goal for a commercial product. Accordingly , the Grieve et al. reference does not cure the deficiencies of the Van Ness et al. reference.

Claims 6-13, 16, 19-21, and 30-32 have been rejected under 35 U.S.C. 103(a) as being obvious over Nagai et al. (U.S. Patent No. 5,194,372) in view of Grieve et al. (U.S. Patent No. 6,391,569). This ground of rejection is respectfully traversed.

The Examiner states that Nagai et al. teaches methods for detecting disorders through the use of fine particles in solution containing immobilized strands of nucleic acid. The probes are

complementary to first and second regions of the target molecule. The particles of Nagai et al. are defined as polystyrene beads having a diameter of 300 nm. See Col. 8, lines 41-60 of the reference.

Nagai et al. does not disclose the formation of a colloidal suspension of nitrocellulose, polyvinyl fluoride or activated nylon for producing particles of defined dimensions for attachment to a biomolecule. Moreover, the reference also fails to disclose the use of blocking molecules in the colloidal suspension for the purpose of blocking non-specific binding sites on the surface of the biomolecule. These are claimed features of the present invention.

Finally, although the Examiner states that a reduction in particles size is a matter of design, applicant notes that the reference is silent as to the method of preparation of the particles, i.e. there is no disclosure of any method for forming particles this small. Absent such disclosure, and accompanying motivation, there is no support for the Examiner's general conclusion.

The Grieve et al. reference has been discussed above, but is not deemed to cure the deficiencies of the primary reference.

Claims 6-16, 18-21 and 30-32 have also been rejected under 35 U.S.C. 103(a) as obvious over Delair et al. (U.S. Patent No. 6,033,853) in view of Grieve et al. (U.S. Patent No. 6,391,569). This ground of rejection is traversed.

Delair et al. describes kits for detecting specific target nucleic acid sequences using labeled probes. The kits include a suspension of insoluble particles bound to identical oligonucleotides. The suspension is further described as comprising latex particles in water wherein the particles range in size from 50 nm to 5 µm in size. See col. 3, lines 30-60 of the reference. The latex of Delair et al. is prepared from a vinyl monomer, such as styrene, rather than from nitrocellulose, activated nylon, or polyvinyl difluoride, as required in the present claims. Note that the function of the latex in the kits of Delair et. al. is to bind the probe to the molecules of interest (col. 3, lines 12-25), whereas the biomolecules of the present invention are designed to function as probes rather than as intermediate coupling molecules. As a final point of distinction, there is no discussion in Delair et al. concerning the use of blocking agents for the probes in the colloidal suspension.

The Grieve et al. reference has been previously discussed, and does not remedy any of the shortcomings of the Delair et al. reference.

Claims 6, 10-13, 16, 19-21 and 30-32 stand rejected under 35 U.S.C. 103(a) as obvious over Kawaguchi et al. (U.S. Patent No. 5,122,600) in view of Grieve et al. (U.S. Patent No. 6,391,569). This ground of rejection is traversed.

Kawaguchi et al. discloses DNA-immobilized microspheres for the specific binding of proteins, and a carrier having a particle size of from about 0.01  $\mu\text{m}$  to 50  $\mu\text{m}$ . The carrier particles of the reference are formed from hydrophilic polymers selected on the basis of their ability to absorb proteins. Col. 3, lines 25-56. The polymers of the reference are basically acrylic polymers and copolymers, and do not include nitrocellulose, polyvinyl difluoride or activated nylon. In addition, and as mentioned above in connection with other references, there is no disclosure in Kawaguchi et al. about the use of blocking molecules in the colloidal solution for non-specific binding to the probe for increased assay sensitivity.

The Grieve et al. reference is not deemed to correct the deficiencies of the Kawaguchi et al. reference as discussed herein.

Claims 6-16, 18-21 and 30-32 have been rejected under 35 U.S.C. 103(a) as obvious over Seul (WO 97/40385). This ground of rejection is also traversed.

The Examiner states that the Seul reference teaches the manipulation of colloidal particles ranging in size from 1 to 10 microns. The particles can include a plurality of molecules, which can be oligonucleotides or proteins, and the colloid can also include labeling agents.

Applicant points out that the instant claims embrace particles having an average size of less than the 1 to 10 micron particle size range recited in the Seul reference. In addition, Seul does not teach or suggest the use of blocking molecules in the colloidal suspension for the purpose of eliminating non-specific binding of the molecular probes.

In view of the foregoing facts and reasons, the present application is now believed to overcome the remaining rejections, and to be in proper condition for allowance. Accordingly, reconsideration and withdrawal of the rejections, and favorable action on this application, is solicited. Entry of the foregoing amendment is deemed appropriate at this time since it serves to advance the prosecution of the application without creating any new issues thereby. The

Examiner is invited to contact the undersigned at the telephone number listed below to discuss the status of this application.

Respectfully submitted,

by William G. Gosz  
William G. Gosz  
Reg. No. 27,787  
Ropes & Gray  
One International Place  
Boston, MA  
Attorneys for Applicant(s)  
Tel. No. (617) 951-7000

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